American Academy of Pediatrics

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February 2, 1998

Michael A. Friedman, MD
Lead Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Room 14-71
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Dear Lead Deputy Commissioner Friedman:

President Clinton recently signed the Food and Drug Administration Modernization and Accountability Act into law (PL 105-115). This presents an opportunity to advance therapies for infants, children, and adolescents in addition to adults. The American Academy of Pediatrics (AAP) makes several recommendations to the Food and Drug Administration as you prepare for the important task of drafting regulations to implement the law.

GENERAL RECOMMENDATIONS:

Include "infants, children and adolescents" explicitly in regulatory language: On behalf of the 53,000 pediatricians represented by the American Academy of Pediatrics, I write to strongly urge that throughout the process of drafting regulations for each component of this law, reference to "infants, children and adolescents" be explicitly incorporated in the language in all sections of PL 105-115 that may apply to this population. Specific recommendations include, but are not limited to, the following sections:

Section 111 - Pediatric Studies of Drugs
Section 120 - Scientific Advisory Panels
Section 127 - Pharmacy Compounding
Section 128 - Reauthorization of Clinical Pharmacology Program
Section 129 - Regulations for sunscreen products
Section 130 - Reports of postmarketing approval studies
Title II - Improving Regulation of Devices
Section 401 - Dissemination of information on new uses
Section 406 - Food and Drug Administration Mission and Annual Report
Section 412 - National uniformity for nonprescription drugs and cosmetics

Historically, children have been the catalyst for changes to the Food, Drug and Cosmetic Act yet they have received only limited benefits from these changes. One need only look the 1962 Kefauver-Harris amendments to the Act to illustrate the point. The 1962 amendment, which requires that drugs must be demonstrated to be safe and effective for their intended uses, came about after

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babies were born with physical deformities resulting from maternal ingestion of thalidomide during pregnancy. Despite the requirement that the safety and effectiveness of drugs be known, as of 1997 only 20 percent of drugs used for children have been labeled for use by infants and children.

Establish an independent Pediatric Advisory Committee. The independent pediatric advisory committee (PAC) assembled by FDA should be a working group of pediatric experts external to FDA with in-depth knowledge of the pharmacological issues related to drugs and biologicals. To ensure that the committee can efficiently function, it should be limited to a total membership of 10-12 persons. The majority of the membership (7-8) should represent pediatric clinicians, pediatric pharmacologists, researchers, and ethicists. The remainder of the committee would include industry representation (2-3) and parent/guardian or child advocate/s(1-2).

The PAC should meet on an as needed basis but no less than twice a year.

Role of PAC would be to advise the FDA on such issues as:

- Accept or reject request for waiver of conducting pediatric studies of new molecular entities (NMEs);
- Determine which already marketed drugs need pediatric studies by relying on a prioritized list of already marketed drugs needing pediatric studies and by seeking input from experts in specific areas of pediatric practice. An organized structure of leaders to serve as resources include the American Academy of Pediatrics, US Pharmacopoeia Pediatric Panel, Pediatric Pharmacology Research Unit Network, AAP specialty sections and others;
- On a case by case basis, determine if a drug is considered as "widely used" in children and if the severity of illness warrants approval;
- Accept or reject waiver requests on the basis of failure to develop formulations;
- Determine the relevant pediatric age groups to be studied for the proposed indications;
- Determine when deferrals of submission of some/all required pediatric data is appropriate until after approval of the product for adults;
- If a pediatric study is deferred, establish appropriate timetables for completion of pediatric studies (e.g., when should a drug enter into pediatric trials).

In addition, the FDA should make appointments of at least one pediatric expert with in-depth knowledge of pharmacological issues within the scope of each of the Advisory Committees that exist within the Center for Drug Evaluation and Research. With the exception of the Advisory Committee on Fertility and Maternal Health, virtually every other Advisory Committee has implications for the pediatric population.

Studies for Pediatric Patients should rely upon approval through an FDA or HHS approved Institutional Review Board (IRB). To insure the safety of children, it is important to avoid making an industry of studies in children in which parents are paid for "volunteering" their children to participate in studies that are approved by IRBs which do not satisfy the requirements developed by the FDA, HHS and AAP for ethical study of drugs in children.

Section 111 - PEDIATRIC STUDIES OF DRUGS

AAP urges that detailed regulations for the pediatric studies of drugs provision (Sec. 111) of PL 105-115 be a top priority.

Definition of "may produce health benefits" should be broad. A drug should meet this definition if it was intended for treatment of a disease, condition or indication which occurs in infants or children. This definition should be construed very broadly.

Define scope and goals of study protocols -- both for new and already marketed drugs -- so that the data would be sufficient to support pediatric labeling in an NDA or SNDA. The intended goal of this provision is to get more drugs labeled for pediatric use. As Representative John Dingell, ranking minority member on the House Commerce Committee noted in remarks on the House floor during consideration of the conference report on S. 830, "Market incentives are included in the bill to encourage pediatric studies, so that labeling of these products will be useful to pediatricians." Even though the law does not specifically call for studies to result in labeling, we urge that studies be extensive enough and of sufficient quality to allow the drug to undergo labeling.

Further, because the written request will be a basis for whether the Secretary accepts or rejects studies that a company does without an agreed upon written protocol the request should be extensive. The AAP recommends the following information be included in a written request for studies:

- -- scope of studies requested will be indication and drug specific and should include input from the Pediatric Advisory Committee;
- -- age groups that need to be studied;
- -- type of prior data that would be acceptable;
- -- number of children/percentage of completion rate for each study;
- -- type of study (e.g., length, PK, safety and efficacy where appropriate ,etc.);
- -- If additional efficacy trials are needed, the size and number of additional independent trials should be stipulated;
- -- timeframe for completing study
- -- location of the trial sites
- -- if studies in a particular age category require a new formulation, completion of the study must include development of that formulation
- -- scope/content of report that will be submitted to the Secretary
- -- sponsor provide analysis of published information of the medication as used in children

It is important that the Secretary have criteria for determining when pediatric studies DO NOT meet a written protocol. Sec. 111 (d)(3) indicates that "The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, have been conducted in accordance with

commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing."

Therefore, the AAP recommends that criteria be established and include:

- -- if studies don't yield data on adequate number of pediatric patients;
- -- data is uninterpretable because of a problem with technical analysis;
- -- sponsor fails to complete studies in the pediatric age groups identified in the written request;
- -- "commonly accepted scientific principles and protocols" should be defined as meeting all existing GCP and GLP standards as well as all current regulatory standards for studies intended to support an NDA or SNDA submission.

Prioritization of already marketed drugs. This list should be developed in consultation with groups represented on the Pediatric Advisory Committee. Criteria for selection of drugs should include severity, morbidity, mortality of condition for which drug is intended, documented or anticipated use in children, therapeutic index (e.g., risk of adverse effects), presence or absence of equivalent drug already available and labeled for children, and number of children impacted by drug. The list should be developed by various drug categories (e.g., antimicrobials, antiarrhythmics, vasopressor, sedatives, hypnotics, psychiatric drug, etc.) and prioritized by various factors (e.g., number of prescriptions written each year in children, if the pharmacokinetics are likely to be different in various pediatric populations, special susceptibility of a population to drug toxicity due to differences in pharmacokinetics, etc.)

Regulations need to clarify congressional intent that doing one study in one pediatric population <u>does not</u> qualify the sponsor for the marketing exclusivity. The definition of pediatric studies means at least one clinical investigation (that at the Secretary's discretion, may include pharmacokinetic studies) in all pediatric age groups in which a drug is anticipated to be used.

Studies in the pediatric population may need to be conducted in patients ranging from premature infants to adolescents. Otherwise, we will end up "orphaning" certain groups, as has been the case in the past. For example, studies in 12-16 year olds will not suffice for toddlers or infants.

Defining the population for study by age may not address important developmental changes in pharmacokinetics and pharmacodynamics. Specifically, at one month of age when the neonate is considered an infant by conventional definitions, a 25 week gestation newborn would only be 29 weeks developmental age and still quite immature. It is most appropriate with the newborn to refer to either developmental age or post conception age where full term is considered 40 weeks. Infancy should start at 44 weeks post conceptional age.

"Anticipated use" (Sec. 111(g)) will need to be determined indication by indication and drug by drug. It must be determined with advice from the Pediatric Advisory Committee to

avoid situations in the past in which FDA or a sponsor, in absence of pediatric expertise, arbitrarily determined a drug would not be used in pediatrics when it was clear it would be or was actually being used. A determination of current use of drugs in off-label treatment should be based upon data from both inpatients and outpatients.

It is essential that drug manufacturers not be the sole determinate of use of a drug in the pediatric population. Surveys from children's hospitals using actual drugs dispensed can provide age related data regarding the use of medications off-label, and this should be updated annually. Surveys of pharmaceutical data and prescriptions from large pediatric populations in the outpatient setting may be provided by HMOs or large pediatric treatment organizations. These data should also be updated annually.

Development of age-appropriate formulations is within the spirit and scope of the definition of pediatric studies. Requirement for formulation that is appropriate for the age should be an integral part of the requirement to conduct pediatric studies. Pediatric studies are irrelevant if the drug is never marketed in a formulation appropriate for children or the formulation used in the studies.

Section 113 - DATA BANK FOR STUDIES FOR SERIOUS ILLNESSES

This data bank can be a useful tool for pediatricians, families and children. It must include specific information about infants, children and adolescent. AAP recommends:

- -- The Pediatric Advisory Committee should determine which pediatric studies should be included in the data bank;
- -- Studies of less serious disorders be included when pediatric patients and families may benefit from data bank information;
- -- Regulatory language should incorporate a specific pediatric protocol section as part of the data bank. In addition, each protocol should include a specific notation that children did -- or did not -- participate in the protocols (similar to the pediatric page on drug labels)

Section 401 - DISSEMINATION OF INFORMATION ON NEW USES

The AAP remains concerned that efforts to directly disseminate information to physicians about pediatric off-label uses of drugs may be a disincentive to securing appropriate labeling of drugs for children and adolescents. In an effort to minimize any potential negative outcome from this provision, the AAP strongly urges the following:

- -- specific references to pediatric populations should be included as part of the information which manufacturers include in a prominently displayed statement.

-- pediatricians should be a subcategory of providers identified who receive off-label information. This will also assist in the development of the Institute of Medicine study that is required by Congress;

-- as part of the SNDA provision, specific language should be included indicating that studies for children are underway, or will begin within a certain timeframe, if the drug will likely be used in children.

As stated above in comments related to "anticipated use of a drug"(page 4, paragraph 6), it would be essential that drug manufacturers not be the sole determinate of use of a drug in the pediatric population.

Section 409 - CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS

The AAP would encourage that regulations include language that would allow funds to be used to study "off patent" drugs which otherwise are difficult to study in pediatric populations.

Thank you for your consideration of these recommendations. The American Academy of Pediatrics is eager to assist the FDA in the development of regulations that will lead to better and more effective drug, biologic and device therapies for infants, children and adolescents.

Sincerely,

/S/

Joseph R. Zanga, MD, FAAP
President

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March 11, 1998

TO: Murray Lumpkin, MD
Deputy Director, Center for Drug Evaluation and Research
American Academy of Pediatrics

FROM: Bob Ward, MD
Chair, Committee on Drugs
American Academy of Pediatrics

SUBJECT: **FOLLOW-UP ISSUES WITH FDA**

The following comments are in follow-up to the teleconference between AAP and the FDA on February 11, 1998 at which we discussed the February 2, 1998 letter from the American Academy of Pediatrics to the FDA regarding implementation of the Food and Drug Administration Modernization Act of 1997. We would appreciate the opportunity to enlarge upon some of the topics that we did not explore in depth during these discussions.

The List of Medications Required by the FDA Modernization Act of 1997

Recognizing the goal of increased study of drugs in children and increased labeling of medications for children, the American Academy of Pediatrics recommends that a comprehensive and broad list of medications qualify for study. The fundamental purpose of this provision of the law is to stimulate as much scientific study of medications in children, as possible. FDA approved drugs number in the thousands. To suggest that a few hundred drugs need to be studied in the pediatric population is a reasonable and appropriate use of resources.

The Academy recommends that the list represent opinions from all areas of pediatric medicine. The AAP provides representation of all pediatric sub-specialists through its numerous Committees and Sections. This is not the only means of determining the therapeutic needs of various pediatric populations, but it will include clinical leaders in each of the areas of pediatric sub-specialty care. The AAP Committee on Drugs and Section on Clinical Pharmacology and Therapeutics could assist with coordinating responses from the various AAP committees and sections.

Several additional recommendations related to the list include:

- Since this legislation applies to both new and already marketed drugs, the medication needing study should be identified by name and since the clinical need often reflects need by therapeutic class, such as H2 or calcium blockers, the therapeutic class and indication (such as antihypertensive) should be

- identified, as well. The market place and competition among industry representatives can determine how many drugs will be or need to be studied and labeled in each therapeutic class and for each indication.
- The list should include all the age categories for which pediatric studies are needed (e.g., newborns, 0-2 years, etc.) This recognizes the potential problem of omission of the youngest ages from studies. We need to keep reminding ourselves that newborns and infants have exhibited the most frequent and most severe side effects from treatment with medications without study. Newborns and infants should therefore, be addressed specifically in requests for studies. Eventually, this should demonstrate to everyone that it is feasible to study medications in these patients.
- The list should be a working document and be accessible for frequent updating (e.g., monthly, quarterly, semi-annually). This is important to stimulate pediatric studies of drugs with patents that will soon expire.
- A process for petitioning for the addition of drugs to this list should be developed. This would allow various interested parties with expertise to suggest in a timely manner drugs that may improve the health care and therapeutic management of children. Also, even though the list may include several members of a particular therapeutic drug class, additional drugs should be eligible for listing if they represent important therapeutic improvements for children. This approach to updating and maintaining the list of medications for study should provide representation from both industry and pediatric patient care providers and best serve the needs of children.

Need for Pediatric Advisory Council

AAP is pleased with FDA's willingness to include a pediatric expert on each CDER Advisory Committee. This is an important step forward. However, AAP has concerns that a "one voice/one vote" approach to pediatric populations will excessively dilute pediatric expertise and inadequately represent pediatric interests.

Even with pediatric representation on individual committees, there is a need for a formalized approach to the broader issues within pediatrics (including devices, assistive technology, biologicals, age groups to be studied, etc.) that may not be met in trying to piece together pediatric experts from existing CDER committees.

AAP appreciates the constraints the FDA is under in setting up new Advisory Committees but strongly urges the FDA to press for a pediatric specific expert panel that can be convened on a semi annual basis to review critical issues related to pediatrics. It is essential that the panel include a breadth and depth of knowledge in order to provide appropriate representation of therapeutic needs from all areas of pediatrics for guidance to the FDA. The experts may vary, depending on the issues at hand. There must be sufficient flexibility in the process of calling together the panel so that the representation yields the needed information.

The Nature and Scope of Pediatric Studies

The intent of the new law is to improve pediatric practice for the ultimate health benefit of children and adolescents. To that end, any study that is adequate to support pediatric labeling for

the relevant indications and age groups should qualify for extension of patent exclusivity. The 1994 rule that was intended to stimulate labeling illustrated that pediatric studies may be conducted, yet not be adequate to qualify for labeling. Any study that is adequate for labeling should certainly receive the reward of extended market exclusivity.

Formulations: Depending on the drug and the age population/s that need pediatric studies, there may be a need for developing a formulation as part of the study (such as development of a liquid preparation where one was not available before). Formulation should be part of study requirements when necessary for the target population. Historically, the lack of age-appropriate formulations has been a significant block to getting drugs studied and labeled for children. The FDA should consider whether development and testing of a new formulation that is more than a change in concentration should qualify for market exclusivity extension.

Completion of studies: The standard for "completion of the study" should include not only the submission of data but a requirement that the data be analyzed, assessed, interpreted, judged and accepted by FDA. The mere completion of a study in children should not necessarily qualify for extension of market exclusivity. Studies must adhere to principles of scientific investigation that utilize adequate and generally accepted study design and population size needed to accurately describe a drug's age-specific kinetics, metabolism, effects, and safety. If the work load at FDA delays review for several months, completion should be dated from the time of submission if the data are found to be acceptable.

Commonly accepted scientific principles and protocols: AAP would urge the FDA to set criteria, as part of the written request for pediatric studies, consistent with its long term commitment to high standards for investigation of drugs and meeting all existing GLP and GCP standards. Criteria should also meet all current regulatory standards for studies intended to support an NDA or SNDA submission. Specific considerations should include, but not be limited to inclusion of an adequate number of pediatric patients to determine the outcome, how to handle a study when data are uninterpretable because of a problem with technical analysis, and how to deal with failure of the sponsor to complete studies in all the pediatric age groups identified in the written request.

Thus, pharmaceutical companies should not be able to completely control the process and extend market exclusivity for studies in children that may be inadequate in power to accurately reflect kinetics, establish optimal dose, or assess the outcome variables.

Tracking of Label Changes

To evaluate accurately and insightfully the changes produced by the proposed rule, as well as the FDA Modernization Act of 1997, AAP would urge the FDA to use a tracking mechanisms that evaluates the number and nature of label changes for pediatric patients. It is important to distinguish extension of labeling to include new, especially younger, age ranges that have not had dosing and efficacy guidelines from changes in wording within the label that may be important, but much less significant for the use of drugs in pediatric patients. Development of new liquid

formulations should be tracked, in particular, since this directly addresses the needs of the most susceptible population.

AAP recommends that the ages affected by labeling changes be captured in this evaluation, as well, e.g. newborn, 0-2 yr., 2-6 yr., 6-12 yr., and >12 yr.

Study Results

Although current regulations require the reporting of adverse affects of medications during investigation for the protection of the patient and the company, ineffective treatment must be reported as well. This ensures that pediatric patients will not receive medications demonstrated to be ineffective and thus be deprived of a more effective treatment while receiving one that has been demonstrated not to be effective. In other words, labeling should reflect when a drug is not effective for a pediatric indication or age group when that information is based on well controlled studies.

Significant consideration must be given to what becomes of the data, particularly if the data have a negative impact on drug use. Avenues of disseminating this information must be explored.

Several other considerations from FDAMA include:

- Addressing issues surrounding companies that may have adequate labeling data but do not want to label based on liability issues. Companies may take the view that it is easier to remain silent because the increase in pediatric use does not outweigh the perceived liability cost.

- Establishing a registry of pediatric studies underway (perhaps through Section 113 of PL 105-115 - Data Bank for Studies for Serious Illnesses). Pediatricians and other health professionals who know that studies were in progress, may continue to be advocates for their timely completion and for the timely release of the data.

- While AAP truly believes industry shares the common goal of getting the most drugs studied and appropriately labeled for pediatric use, there is a concern that economic considerations will drive the selection of drugs which the industry will agree to study from the prioritized list. The highly profitable drugs with widespread use in adults, especially those whose patents are close to expiring, will be the likeliest candidates for study while important drugs that are less profitable may be left behind.

  A strategy to address this concern might be to "partner" profitable drugs with less profitable drugs which are manufactured by the same sponsor to discourage a purely economic approach to pediatric studies. All drugs which complete studies under this provision of the law -- whether "partnered" or free standing -- would receive market exclusivity provisions.

- Another consideration is to initiate some public recognition of companies that undertake investigations in the newborn, especially, but also in infants and children under six years of

age. Annual publication of the number and type of label changes should help to reward companies for their efforts.

BW:ch

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